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Task Force on Harmonisation of Classification and Labelling

Ad Hoc Expert Group on Target Organ Toxicity

ISSUE DOCUMENT NO 4 : REVERSIBLE AND IRREVERSIBLE EFFECTS

2nd Meeting of the ad hoc Expert Group on Target Organ Toxicity,
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ISSUE DOCUMENT No 4: REVERSIBLE AND IRREVERSIBLE EFFECTS

ISSUE

1. Should the scope of the target organ toxicity endpoint include both reversible and irreversible effects?

CURRENT SITUATION

EU

2. Included in the EU definition of serious damage to health is death, toxicologically significant, clear functional disturbance or morphological changes caused by repeated or prolonged exposure by an appropriate route. Particularly important are the irreversible changes.

3. The EU legislation considers that the following factors, for example, would be included in "evidence of target organ toxicity"

- major functional changes in the central or peripheral nervous systems, including sight, hearing and sense of smell
- consistent changes in clinical biochemistry, haematology, or uninalysis parameters
- severe organ damage noted on microscopic examination following autopsy
- widespread necrosis, fibrosis or granuloma formation in vital organs with regenerative capacity,
- severe morphological changes that are potentially reversible but are clear evidence or marked organ dysfunction (e.g., severe fatty change in the liver) and
- evidence of appreciable cell death in vital organs incapable of regeneration.

4. The EU legislation further considers that the following effects, for example, would not be considered as evidence of target organ toxicity

- clinical observations or changes in bodyweight gain, food consumption or water intake which may have some toxicological importance but which do not, by themselves, indicate "serious damage",
- small changes in clinical biochemistry, haematology or urinalysis parameters which are doubtful or minimal toxicological importance,
- changes in organ weights with no evidence or organ dysfunction;
- adaptive responses

US CPSC

5. The US CPSC defines a chronic health effect as a persistent toxic effect that develops over time from a simple, prolonged or repeated exposure. The persistent effects may be reversible or irreversible.

US OSHA

6. OSHA defines "chronic effects" as generally occurring as a result of long-term exposure and are of long duration. Examples of chronic effects include hepatotoxins, nephrotoxins, neurotoxins, agents

which act on the blood or hematopotoietic system, agents which damage the lung, chemicals which irritate the pulmonary system.

Canada/WHMIS

7. WHMIS defines chronic toxic effect as adverse effect to the health of a person or test animal that develops, over time, following a single exposure to a toxic substance or from prolonged or repeated exposure to a toxic substance under conditions that do not produce that effect from a single exposure. A substance is classified as having a chronic toxic effect if it elicits a response of sufficient severity to threaten life or cause serious permanent impairment in a statistically significant proportion of the test population.

SIMILARITIES AND DIFFERENCES

8. All systems, except the Canadian workplace system, consider both irreversible and reversible effects to be included in this classification endpoint.

POSSIBLE APPROACHES

9. Some of the possible approaches for this issue include

- Consider only irreversible effects to be included in the endpoint.
- Consider irreversible and reversible effects, which are not transient.
- Consider both reversible and irreversible effects for the endpoint.

DISCUSSION

10. The common theme in all of the systems regarding inclusion of adverse health impact on organ(s)/systems is to include effects that cause functional impairment in humans. These effects can be reversible as well as irreversible, and from single, prolonged or repeated exposure.

11. All systems are intended to exclude minor changes in physiological parameters which may be transient or permanent such as weight gain, changes in the clinical biochemical, haematology, urinalysis, small changes in the organ weight without organ/systemic dysfunction, and adaptive responses.

12. There are numerous adverse effects on human health which are reversible, but nevertheless during their manifestation, i.e. normally during or immediately following exposure, the effects are serious enough to be of concern for human health, well-being and/or safety. Examples include transient narcotic effect, neurobehavioural changes, neuromuscular impairment, neurotoxicity, impairment of special senses, haematological changes (methaemoglobinaeia, carboxyhaemoglobinaemia, anaemia), immunotoxicity, impairment of spermatogenesis, endocrine disruption. Whilst these effects are present normal functionality is impaired and this situation can have consequences ranging from transient reduced capability to transient complete inability that could in fact be life-threatening.

13. Some adverse effects which are reversible and which are also transient can be considered very serious; e.g. adverse effects on any part of the nervous system in circumstances where alertness and

unimpaired co-ordination are essential, adverse effects on any part of the immune system to prevent the establishment of serious disease (or indeed the promotion of an auto-immune disease), adverse effects on any part of the endocrine system which impairs normal physiological control (could lead to some forms of cancer) or impairment of fertility (transient loss of fertility is still loss of fertility).

14. If the intent is to use the systemic target organ endpoint to classify well-substantiated long term effects not handled under other endpoints (e.g. carcinogenicity, reproductive effects), it would be best to delineate the endpoint broadly. One can list several examples of effects which might be missed if the criteria for duration of target organ toxicity are too rigid.

- Substances causing significant liver damage which is generally reversible if exposure is stopped should be included.

- Substances releasing carbon monoxide can lead to carboxyhemoglobin which can cause severe harm or death should be included, even though the biological half-life of COHb is about 18 hours.

- This may be an appropriate place to include the adverse effect(s) (signs and pathology) that may not have contributed to the LD50 because it occurred late or was not severe enough to cause mortality after a single exposure but could cause functional impairment in humans. (See also Issue Document No 1 on single, prolonged or chronic exposure)

15. If we plan to single out for exclusion from the target organ toxicity endpoint those effects that are long term or irreversible, but are caused by a single exposure, two issues arise:

a. Available human or animal data does not generally allow regulators to distinguish between long term effects caused by a single dose or by repeated exposure. That is, repeat dose animal studies will show an effect from repeated doses, but a separate experiment would be needed to identify if the effect could have been caused by only a single high dose. Since acute studies have a maximum duration of 14 days, they are not suitable to answer this question. (See also the issue paper on single exposure).

b. If we exclude chemicals known to cause serious effects following a single exposure from this endpoint, it is hard to draw the line for other chemicals may cause long term effects from short term, rather than single exposures. (See also the issue paper on single exposure).

CONCLUSION

16. Under target organ toxicity effects that can cause functional impairment in humans should be included whether it is reversible or irreversible (Possible Approach 3). Changes such as physiological parameters which may be transient or permanent (e.g. weight gain), changes in the clinical biochemical, haematology, urinalysis, small changes in the organ weight without organ/systemic dysfunction, and adaptive responses should not be included.